Remarks

Claim 33, 41, and 55 have been amended to recite a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is capable of sublingual or buccal absorption through the mucous membranes of the mouth (due to a sufficient resonance time and sufficiently low molecular weight for uptake in the oral cavity) in a therapeutically effective level; and a second oral portion located within the first portion which contains a pharmaceutically active ingredient which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved. Support for the amendments is found at page 7, lines 17-20 and at page 18, lines 21-26 and page 25, lines 10-14.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 55-57 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner alleges that claim 57, which depends on parent claim 55, does not further limit the parent claim. Such an assertion is incorrect. Claim 55 recites specific active agents in a Markush group. Claim 57 further limits the active agents recited in the Markush group in claim 55 to those active agents having a molecular weight less than 350 Daltons. Claim 55 recites several active agents with a molecular weight greater than 350 Daltons. For example, Buprenorphine has a molecular weight of 468 Daltons; Aceclofenac has a molecular weight of

354 Daltons; and Buspirone has a molecular weight of 422 Daltons. Therefore, it is clear that claim 57 further limits claim 55 by limiting the members of the Markush group to those compounds which have a molecular weight less than 350 Daltons.

Rejection Under 35 U.S.C. § 103

a. Sterling in View of Powell and Frömming

Claims 33-39, 42-50, 52-53 and 55-57 were rejected under 35 U.S.C. § 103(a) as obvious over GB 800,973 to Sterling ("Sterling") in view of U.S. Patent No. 6,140,319 to Powell ("Powell") in further view of DE 3338978 to Frömming ("Frömming"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998)

(The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, the indicating lamination having an outer medicinal layer which is soluble in the patient's mouth. Sterling does not disclose a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level, wherein the active ingredient is selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine,

Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, *being present in an amount between 1 micrograms and 50 mg*, and having a rapid onset following intraoral administration. Sterling also fails to disclose a second component which is either chewable or provides sustained release.

Powell describes the use of one or more vasopeptidase inhibitors to treat and/or relieve the symptoms of angina pectoris (col. 1, line 65 to col. 2, line 1). Preferred vasopeptidase inhibitors include omapatrilat and BMS 189,921. Typical dosages of the vasopeptidase inhibitors for treating angina range from 0.1 mg/kg to about 0.2 mg/kg, preferably from about 0.3 mg/kg to about 2.0 mg/kg (col. 3, lines 43-47). The vasopeptidase inhibitor(s) may be employed in combination with one or more pharmaceutically acceptable agents known to be useful in the treatment of angina such as long-acting nitrates such as nitroglycerin; β-adrenergic blocking agents such as propanolol hydrochloride, timolol maleate, carvedilol, and metoprolol tartrate; calcium entry blockers such as amlodipine besylate, diltiazem hydrochloride, and verapamil hydrochloride; and antiplatelet agents (col. 4, lines 5-15). Powell does not disclose or even suggest a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level; and a second oral portion located within the first portion which is released for uptake into the intestine in a therapeutically

effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation.

The Examiner alleges that it would have been obvious to one of ordinary skill in the art to look to the teachings of Powell and utilize the instant verapamil in place of Sterling's nitroglycerin since Powell teaches that both compounds are used to treat angina. Such an assertion is incorrect. Powell describes pharmaceutical compositions containing a vasopeptidase inhibitor, namely omapatrilat or BMS 189,921, alone or in combination with another class of pharmaceutically active agents known to be useful in the treatment of angina. One aspect of the applicant's invention is the observation that compounds having a sufficiently low molecular weight (less than 350 Daltons) or certain structural features can be released for uptake in the oral cavity. Powell does not disclose or even suggest a relationship between molecular weight and/or structural features and uptake in the oral cavity. Omapatrilat has a molecular weight of 408.5 Daltons and BMS 189,921 has a molecular weight of 380 Daltons. Powell does not disclose or even suggest the use of verapamil or amlodipine for uptake in the oral cavity and Powell is silent regarding the dosages of the coadministered pharmaceutically active agents such as verapamil hydrochloride and amlodipine.

Frömming describes the use of verapamil or gallopamil for sublingual or buccal administration. The verapamil or gallopamil can be administered in a tablet, a chewable capsule or a spray. For the production of sublingual tablets, the concentration of verapamil is from 5 to 25 mg. Frömming does not disclose a pharmaceutical composition comprising a first intraoral

portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level; and a second oral portion located within the first portion which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation.

In summary, the prior art discloses pieces of the claimed composition but not the motivation to combine or modify as applicants have done.

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, the indicating lamination having an outer medicinal layer which is soluble in the patient's mouth, but not the selection of a drug that is rapidly absorbed in the mouth that is released first and a second drug which is released second for uptake in the GI tract.

Powell and Frömming describe the use of one or more vasopeptidase inhibitors to treat and/or relieve the symptoms of angina pectoris, but not the motivation to combine with a second drug that is released later for absorption in the GI tract.

Nowhere does the prior art provide the motivation to combine these elements as applicants have done. It is well established that it is not sufficient to merely identify art and then assert that it would be obvious to combine: the motivation must come from the references.

b. Sterling in View of Powell, Frömming, and Panther

Claims 41, 51, and 54 were rejected under 35 U.S.C. 103 (a) as obvious over Sterling in view of Powell, Frömming, and U.S. Patent No. 6,200,604 to Panther ("Panther"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed above, Sterling in combination with either of Powell and/or Frömming do not disclose nor make obvious the claimed pharmaceutical composition.

d, wherein the second portion is either a sustained release or chewable formulation.

Panther describes a pharmaceutical dosage form comprising an orally administerable medicament in combination with an effervescent agent used as a penetration enhancer to influence the permeability of the medicament across the buccal, sublingual, and gingival mucosa (col. 2, lines 7-11). Panther discloses that the effervescent agent can act to increase the rate and extent of absorption of the active agent by: (1) reducing the mucosal layer thickness and/or viscosity; (2) tight junction alteration; (3) inducing a change in the cell membrane structure; and (4) increasing the hydrophobic environment within the cellular membrane.

The Examiner alleges that it would have been obvious to one of ordinary skill in the art to combine the teachings of Sterling and Panther and utilize an effervescent agent in the rapid onset layer of Sterling to enhance permeation of the drug across the oral mucosa. Sterling is discussed above and describes a two component drug delivery device having a medical core and an intervening taste-indicating alarm layer or lamination, the indicating lamination having an outer medicinal layer which is soluble in the patient's mouth. Sterling does not disclose anything

resembling an effervescent coating containing the first agent to be released. The purpose of the effervescent signaling system is to inform the patient that it is time to swallow or chew the inner core of the composition, ***not*** to enhance the absorption of the active ingredient as disclosed by Panther.

Accordingly, one of ordinary skill in the art would not be motivated to combine the teachings of Sterling in view of Powell, Frömming, and Panther to prepare the compositions recited in claims 41, 51, and 54.

c. Neuser in View of Panther

Claims 41-42, 51, and 54 were rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent Publication No. 2001/0002999 by Neuser *et al.* ("Neuser") in view of Panther. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Neuser describes pharmaceutical compositions which can be administered orally and contain a fixed combination of at least one ***locally*** acting analgesic with a rapid onset of action and at least one systemically acting analgesic with a sustained action.

In contrast, both active ingredients of the applicant's composition are ***systemically*** acting agents that are released into the blood stream at different sites in the human body: the first ingredient within the oral cavity and the second ingredient within the intestine.

As discussed above, Panther does not make up for the deficiencies of Neuser – Panther does not teach that one should select systemically acting agents and put them into a single formulation that releases in the mouth one which is rapidly absorbed through the buccal or

sublingual membranes and one which is released much later, into the GI tract. If one combine Panther and Neuser, one would not obtain the claimed two component formulation. Therefore Panther in combination with Neuser does not make obvious the claimed compositions.

d. Barclay in View of Panther

Claims 33-43 and 49-57 were rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,053,032 to Barclay *et al.* ("Barclay") in view of Panther. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Panther is discussed above.

Barclay describes an ***osmotic*** device for a delivering a drug into the mouth of a human patient (abstract). The device described by Barclay comprises a wall surrounding a compartment housing a layer of an agent that is insoluble to very soluble in aqueous biological fluids such as saliva and a layer of fluid swellable hydrophilic polymer. A passageway in the wall connects the agent with the exterior of the device. The wall is permeable to the passage of aqueous biological fluids but impermeable to the hydrophilic polymer. The device described by Barclay is designed to deliver the ***same*** drug into both the oral cavity and into the GI tract since the device has only ***one*** drug reservoir (see Figs. 1-4 and col. 8, lines 31-35). This device cannot be used to deliver two different drugs as described by the applicants and, therefore, is distinctly different.

Barclay does not disclose the use of a sustained release or chewable formulation which is swallowed. Barclay describes an osmotic device. Indeed, Barclay clearly teaches away from either a sustained release or a chewable second portion. While Barclay describes one

embodiment which contains an HPMC coating, such a coating may ***delay*** release of the second component, but it would not result in ***sustained*** release. Chewing would destroy an osmotic device.

Barclay's device is "designed to be retained in the mouth for periods of time on the order of 0.5 to 12 hours" (col. 7, lines 35-36). The applicants describe a composition wherein the first portion [that contains a drug to be released for uptake in the oral cavity into the systemic circulation] "disintegrates or dissolves within 10 minutes, when the composition is contacted with saliva" (see claim 48). Barclay indeed discloses a variety of drugs that can be delivered using the device (col. 10, line 50 to col. 11, line 35); however, only one drug can be delivered using the device. The drug can ***either*** be intended for uptake in the oral cavity or intended for uptake in the intestine. The applicants' composition allows for administration of drug intended for uptake in the oral cavity ***followed*** by drug intended for uptake in the intestine.

Applicants select and use drugs for uptake within the oral cavity based on their ability to be absorbed through oral mucosa membrane (structural features and/or relatively low molecular weights). Barclay makes no distinction between two different classes of drugs: (a) drugs that are released for uptake in the oral cavity and (b) drugs that are released in the oral cavity and swallowed for uptake in the intestine. Applicants have designed a composition that can deliver drugs from both classes in a single dosage form.

As discussed above, Panther describes a pharmaceutical dosage form comprising an orally administerable medicament in combination with an effervescent agent used as a

penetration enhancer to influence the permeability of the medicament across the buccal, sublingual, and gingival mucosa (col. 2, lines 7-11).

One or ordinary skill in the art would not be motivated to combine the teachings of Barclay and Panther to make the claimed pharmaceutical composition, nor would one obtain the claimed composition by combining Barclay with Panther. Barclay is an osmotic delivery device for releasing a single drug; Panther delivers only a single drug. Indeed, if one combined the effervescent compound of Panther with the device of Barclay one would likely have an exploding device, not a delivery device.

Pertinent Art

The Examiner alleged that U.S. Patent No. 5,702,723 to Griffin is pertinent to the applicants' disclosure. Griffin describes a multi-stage delivery system in the form of a pill having an outer layer comprising an active substance that will dissolve and have a beneficial effect somewhere in the mouth or upper respiratory area with the subsequent layers dissolving and the contained substances acting deeper within the body such as in the gastrointestinal area or systemically (col. 3, lines 8-13). Griffin emphasizes that the saliva or mucous-fluid soluble active agent of an external layer is a locally acting agent providing a condition-related therapeutic effect in the mouth, esophagus or bronchial tract (col. 3, line 65 to col. 4, line 4; col. 6, lines 33-35). The active ingredient of an internal layer is internally or systemically active (col. 6, lines 23-24). In contrast, both active ingredients of the applicant's composition are systemically acting agents that are released into the blood stream at different sites in the human

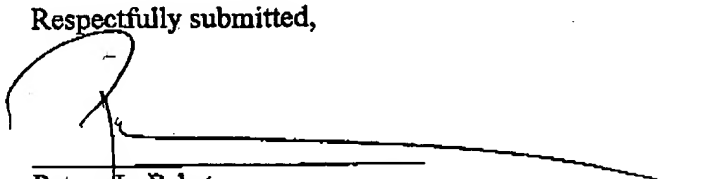
body: the first ingredient within the oral cavity and the second ingredient within the intestine. Griffin is therefore not believed to be of any material relevance.

Double Patenting Rejection

Claims 33, 35, 38-39, 41, 43-44, 46, and 48 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 5-6, 8, 10, and 16 of copending Application Serial No. 10/015930. In response, Applicants will file a terminal disclaimer to overcome the double patenting rejection upon indication that the claims are otherwise allowable.

Allowance of claims 33-57 is respectfully solicited.

Respectfully submitted,



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